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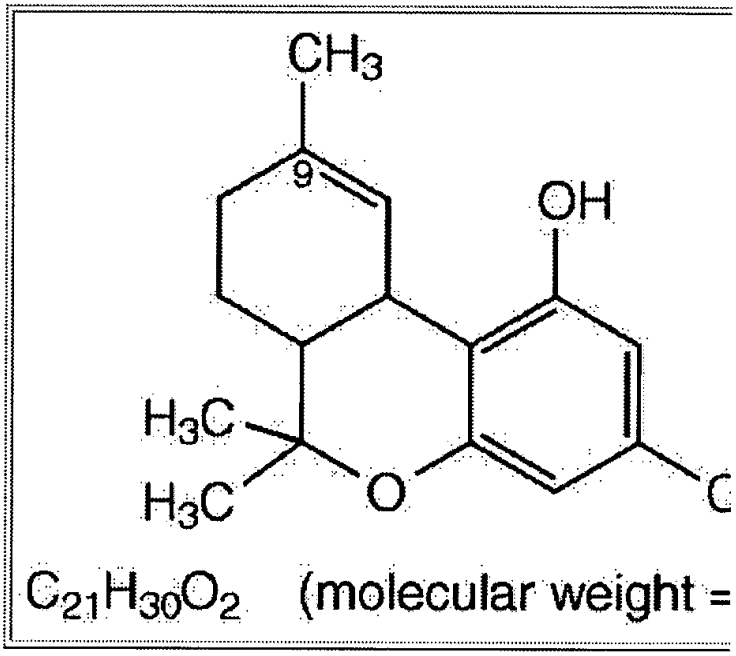
PDR® entry for

MARINOL® (Unimed)
(dronabinol) Capsules
Rx only.

Dronabinol is a cannabinoid designated chemically as (6a *R-tr*
)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- *6H* -dibenz
Dronabinol has the following empirical and structural formulas



Dronabinol, the active ingredient in Marinol, is synthetic delta·
(delta-9-THC). Delta-9-tetrahydrocannabinol is also a naturall
Cannabis sativa L . (Marijuana).

Dronabinol is a light yellow resinous oil that is sticky at room t
upon refrigeration. Dronabinol is insoluble in water and is forn
has a pK_a of 10.6 and an octanol-water partition coefficient: €

Capsules for oral administration: Marinol is supplied as round,
containing either 2.5 mg, 5 mg, or 10 mg dronabinol. Each Ma
formulated with the following inactive ingredients: FD&C Blue
No. 40 (5 mg), FD&C Yellow No. 6 (5 mg and 10 mg), gelatin,
methylparaben, propylparaben, sesame oil, and titanium diox

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CLINICAL PHARMACOLOGY

Dronabinol is an orally active cannabinoid which, like other ca effects on the central nervous system (CNS), including central activity. Cannabinoid receptors have been discovered in neura may play a role in mediating the effects of dronabinol and oth

Pharmacodynamics: Dronabinol-induced sympathomimetic tachycardia and/or conjunctival injection. Its effects on blood but occasional subjects have experienced orthostatic hypotens abrupt standing.

Dronabinol also demonstrates reversible effects on appetite, n and perception. These phenomena appear to be dose-related, with higher dosages, and subject to great interpatient variabil

After oral administration, dronabinol has an onset of action of hours and peak effect at 2 to 4 hours. Duration of action for p 6 hours, but the appetite stimulant effect of dronabinol may c longer after administration.

Tachyphylaxis and tolerance develop to some of the pharmacc dronabinol and other cannabinoids with chronic use, suggestir sympathetic neurons. In a study of the pharmacodynamics of exposure, healthy male volunteers (N=12) received 210 mg/d administered orally in divided doses, for 16 days. An initial ta dronabinol was replaced successively by normal sinus rhythm decrease in supine blood pressure, made worse by standing, v initially. These volunteers developed tolerance to the cardiova adverse CNS effects of dronabinol within 12 days of treatment

Tachyphylaxis and tolerance do not, however, appear to devel stimulant effect of Marinol. In studies involving patients with A Deficiency Syndrome (AIDS), the appetite stimulant effect of M sustained for up to five months in clinical trials, at dosages ra 20 mg/day.

Pharmacokinetics:

Absorption and Distribution: Marinol (dronabinol) is almost c to 95%) after single oral doses. Due to the combined effects o metabolism and high lipid solubility, only 10 to 20% of the ad the systemic circulation. Dronabinol has a large apparent volu approximately 10 L/kg, because of its lipid solubility. The plas dronabinol and its metabolites is approximately 97%.

The elimination phase of dronabinol can be described using a with an initial (alpha) half-life of about 4 hours and a terminal 36 hours. Because of its large volume of distribution, dronabir may be excreted at low levels for prolonged periods of time.

Metabolism: Dronabinol undergoes extensive first-pass hepa by microsomal hydroxylation, yielding both active and inactive and its principal active metabolite, 11-OH-delta-9-THC, are pr equal concentrations in plasma. Concentrations of both parent peak at approximately 2 to 4 hours after oral dosing and decli Values for clearance average about 0.2 L/kg-hr, but are highly

complexity of cannabinoid distribution.

Elimination: Dronabinol and its biotransformation products a and urine. Biliary excretion is the major route of elimination w radiolabeled oral dose being recovered from the feces within 7 with 10 to 15% recovered from urine. Less than 5% of an oral unchanged in the feces.

Following single dose administration, low levels of dronabinol detected for more than 5 weeks in the urine and feces.

In a study of Marinol involving AIDS patients, urinary cannabi concentration ratios were studied bi-weekly over a six week pe cannabinoid/creatinine ratio was closely correlated with dose. cannabinoid/creatinine ratio was observed after the first two v indicating that steady-state cannabinoid levels had been reacl consistent with predictions based on the observed terminal ha

Special Populations: The pharmacokinetic profile of Marinol h in either pediatric or geriatric patients.

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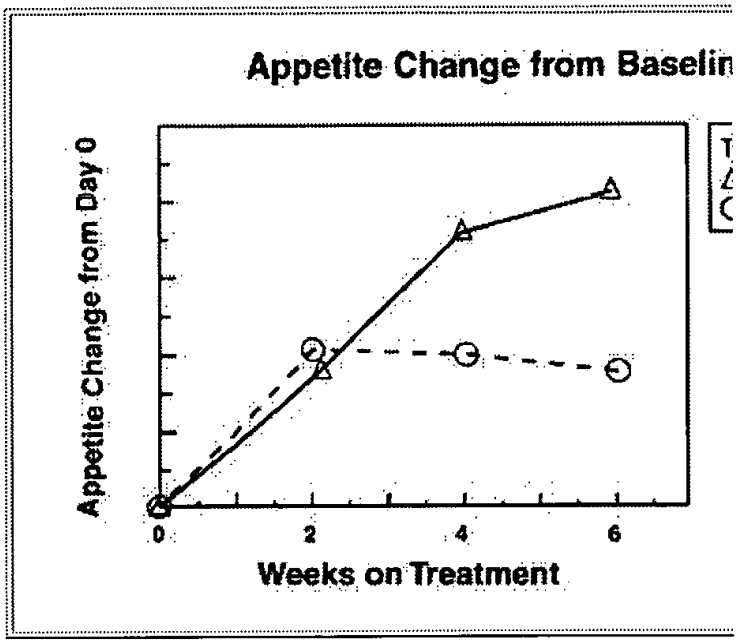
CLINICAL TRIALS

Appetite Stimulation: The appetite stimulant effect of Mari treatment of AIDS-related anorexia associated with weight los randomized, double-blind, placebo-controlled study involving dosage of Marinol in all patients was 5 mg/day, administered hour before lunch and one hour before supper. In pilot studies administration of Marinol appeared to have been associated w frequency of adverse experiences, as compared to dosing later Marinol on appetite, weight, mood, and nausea was measured during the six-week treatment period. Side effects (feeling hig somnolence) occurred in 13 of 72 patients (18%) at this dosag was reduced to 2.5 mg/day, administered as a single dose at s

As compared to placebo, Marinol treatment resulted in a statis improvement in appetite as measured by visual analog scale (toward improved body weight and mood, and decreases in na

After completing the 6-week study, patients were allowed to c Marinol in an open-label study, in which there was a sustainec appetite.



Antiemetic: Marinol (dronabinol) treatment of chemotherap evaluated in 454 patients with cancer, who received a total of of various malignancies. The antiemetic efficacy of Marinol wa receiving cytotoxic therapy with MOPP for Hodgkin's and non-l Marinol dosages ranged from 2.5 mg/day to 40 mg/day, admi divided doses every four to six hours (four times daily). As ind table, escalating the Marinol dose above 7 mg/m ^{2} increased t experiences, with no additional antiemetic benefit.

Marinol Dose: Response Frequency and Adverse
(N = 750 treatment courses)

	Response Frequency (%)			Adverse Ev	
Marinol Dose	Complete	Partial	Poor	None	Nond
<7 mg/m ^{2}	36	32	32	23	
>7 mg/m ^{2}	33	31	36	13	

*Nondysphoric events consisted of drowsiness, tachycardia,

Combination antiemetic therapy with Marinol and a phenothia may result in synergistic or additive antiemetic effects and att associated with each of the agents.

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INDIVIDUALIZATION OF DOSAGES

The pharmacologic effects of Marinol (dronabinol) are dose-re considerable interpatient variability. Therefore, dosage individ achieving the maximum benefit of Marinol treatment.

Appetite Stimulation: In the clinical trials, the majority of with 5 mg/day Marinol, although the dosages ranged from 2.5 adult:

1. Begin with 2.5 mg before lunch and 2.5 mg before supp
   If CNS symptoms (feeling high, dizziness, confusion, sor
   usually resolve in 1 to 3 days with continued dosage.
2. If CNS symptoms are severe or persistent, reduce the d
   supper. If symptoms continue to be a problem, taking tl
   evening or at bedtime may reduce their severity.
3. When adverse effects are absent or minimal and further
   desired, increase the dose to 2.5 mg before lunch and 5
   and 5 mg. Although most patients respond to 2.5 mg tw
   daily has been tolerated in about half of the patients in a
   studies.

The pharmacologic effects of Marinol are reversible upon treat

Antiemetic: Most patients respond to 5 mg three or four tim
escalated during a chemotherapy cycle or at subsequent cycle
results. Therapy should be initiated at the lowest recommende
clinical response. Administration of Marinol with phenothiazine
prochlorperazine, has resulted in improved efficacy as compar
without additional toxicity.

Pediatrics: Marinol is not recommended for AIDS-related ar
patients because it has not been studied in this population. Th
treatment of chemotherapy-induced emesis is the same as in a
recommended in prescribing Marinol for children because of th

Geriatrics: Caution is advised in prescribing Marinol in elder
are generally more sensitive to the psychoactive effects of dru
no difference in tolerance or efficacy was apparent in patients

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INDICATIONS AND USAGE

Marinol (dronabinol) is indicated for the treatment of:

1. anorexia associated with weight loss in patients with AII
2. nausea and vomiting associated with cancer chemothera
   failed to respond adequately to conventional antiemetic

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CONTRAINDICATIONS

Marinol (dronabinol) is contraindicated in any patient who has
hypersensitivity to any cannabinoid or sesame oil.

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WARNINGS

Patients receiving treatment with Marinol should be specificall
operate machinery, or engage in any hazardous activity until i
are able to tolerate the drug and to perform such tasks safely.

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